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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	9

DATE MAILED: 07/31/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/857,069	HAMBURGER ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for R ply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 53-69 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 53-69 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicants' preliminary amendment filed 5-31-01 has been entered. Claims 1-52 have been canceled. Claims 1-17 have been added to substitute the canceled claims. Since claims 1-52 have already existed, the added claims 1-17 have been renumbered to claims 53-69. Claims 53-69 are pending and under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 53-69 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: what is used to transform the multicellular eukaryotic diploid parasite.

3. Claims 53-63 and 65-69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "group transformation method" in claim 53 is vague and renders the claim indefinite. It is unclear as to the metes and bounds of what is considered "group transformation method". The specification only provide some examples of group transformation method, such as electroporation, chemical transformation, lipofection, or particle bombardment (see specification, page 10, lines 3-15), but fails to specifically define the phrase "group

transformation method". Claims 54-63 and 65-69 depend on claim 53 but fail to clarify the indefiniteness.

Claims 65 and 66 recite the limitation "said transgene" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claims 67 and 68 depend on claim 66 but fail to clarify the indefiniteness.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 53, 54, 59, 60, 63-66 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Kim et al., 1997 (US Patent No. 5,643,718).

Claims 53, 54, 59, 60, 63-66 and 69 are directed to a method of genetically modifying a eukaryotic diploid parasite, such as a worm, comprising direct transforming said parasite with a group transformation method, such as electroporation. Claim 63 specifies the parasite is sensitive to a known drug. Claim 69 specifies the parasite has distinguishable sexes.

Kim teaches a method for stable transformation of a parasite of genus Toxoplasma, such as *Toxoplasma Gondii*, by introducing into said parasite a vector containing a DNA sequence encoding a selectable marker, such as CAT, via electroporation and homologous recombination (e.g. abstract, column 23, 24). It was known in the art that *Toxoplasma Gondii* is sensitive to

some antibiotics, such as clarithromycin and pyrimethamine, and has distinguishable sexes. Therefore, claims 53, 54, 59, 60, 63-66 and 69 are anticipated by Kim.

6. Claims 53, 54, 59, 60, 63-66 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Roos et al., 1997 (Methods: A Comparison to Methods in Enzymology, Vol. 13, p. 112-122).

Claims 53, 54, 59, 60, 63-66 and 69 are directed to a method of genetically modifying a eukaryotic diploid parasite, such as a worm, comprising direct transforming said parasite with a group transformation method, such as electroporation. Claim 63 specifies the parasite is sensitive to a known drug. Claim 69 specifies the parasite has distinguishable sexes.

Roos teaches using pyrimethamine resistance vectors derived from Toxoplasma Gondii's bifunctional dehydrofolate reductase-thymidylate synthase (DHFR-TS) gene for very high frequency stable transformation of the parasite *Toxoplasma Gondii* via electroporation of T. gondii tachyzoites and teaches that large genomic constructs integrate at the endogenous locus by homologous recombination (e.g. p. 112, 113, left column). It was known in the art that *Toxoplasma Gondii* is sensitive to some antibiotics, such as clarithromycin and pyrimethamine, and has distinguishable sexes. Therefore, claims 53, 54, 59, 60, 63-66 and 69 are anticipated by Roos.

7. Claims 53, 54, 59, 64-66 and 69 are rejected under 35 U.S.C. 102(b) as being anticipated by Waters et al., 1997 (Annals of Tropical Medicine and Parasitology, Vol. 91, No. 1, p. S63-S67).

Claims 53, 54, 59, 64-66 and 69 are directed to a method of genetically modifying a eukaryotic diploid parasite, such as a worm, comprising direct transforming said parasite with a group transformation method, such as electroporation. Claim 69 specifies the parasite has distinguishable sexes.

Waters teaches using a plasmid transfection vector containing a drug resistant form of DHFR-TS gene from rodent parasite *Plasmodium berghei* for stable transformation into merozoites of *Plasmodium berghei* via electroporation and site-directed integration by homologous recombination into parasite genome (e.g. abstract, p. S64, left column). It was known in the art that has distinguishable sexes. Therefore, claims 53, 54, 59, 64-66 and 69 are anticipated by Waters.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 53-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Miller, 1997 (WO 97/11191) in view of either Kim et al., 1997 (US Patent No. 5,643,718) or Roos et al., 1997 (Methods: A Comparison to Methods in Enzymology, Vol. 13, p. 112-122).

Claims 53-69 are directed to a method of genetically modifying a eukaryotic diploid parasite, such as a flat worm schistosome, comprising direct transforming said parasite with a group transformation method, such as electroporation. Claim 63 specifies the parasite is sensitive to a known drug. Claims 67 and 68 specify the selected genomic locus is a repetitive sequence or a unique sequence. Claim 69 specifies the parasite has distinguishable sexes.

Miller teaches a method of generating genetically engineered schistosome as an intermediate vector for secretion of desired protein, such as therapeutic protein, into the bloodstream of humans and other susceptible hosts via microinjection of the transgene DNA into the pronuclei or cytoplasm of the zygotes of stage I schistosome eggs. "The use of schistosomes as intermediate vector facilitates mass production, quality control, termination of therapy at will and dose titration" (e.g. abstract, p. 38).

Miller does not teach using electroporation, chemical transformation, lipofection, or particle bombardment, and homologous recombination to generate genetically modified schistosome or diploid parasites. Miller does not specifically teach the selected genomic locus is a repetitive locus or a unique sequence.

Kim teaches a method for stable transformation of a parasite of genus Toxoplasma, such as *Toxoplasma Gondii*, by introducing into said parasite a vector containing a DNA sequence

encoding a selectable marker, such as CAT, via electroporation and homologous recombination (e.g. abstract, column 23, 24). Kim also teaches recombinant expression of a desired protein in a host infected with a transformed obligate intracellular parasite of the phylum Apicomplexa (e.g. column 4, lines 22-31). It was known in the art that *Toxoplasma Gondii* is sensitive to some antibiotics, such as clarithromycin and pyrimethamine, and has distinguishable sexes.

Roos teaches using pyrimethamine resistance vectors derived from Toxoplasma Gondii's bifunctional dehydrofolate reductase-thymidylate synthase (DHFR-TS) gene for very high frequency stable transformation of the parasite *Toxoplasma Gondii* via electroporation of T. gondii tachyzoites and teaches that large genomic constructs integrate at the endogenous locus by homologous recombination (e.g. p. 112, 113, left column). It was known in the art that *Toxoplasma Gondii* is sensitive to some antibiotics, such as clarithromycin and pyrimethamine, and has distinguishable sexes.

It would have been obvious for one of ordinary skill at the time of the invention to substitute the microinjection method as taught by Miller with electroporation and homologous recombination as taught by Kim or Roos for stable transformation of a diploid parasite, such as a schistosome, with a vector containing desired DNA sequence because both schistosome and *Toxoplasma Gondii* are parasites and it was well known in the art at the time of the invention to use electroporation for stable transformation of animal cells and to make genetically modified animal including parasites. Random integration of genome via microinjection or site-directed homologous recombination into genome can target repetitive sequences or unique sequences in the genome and those techniques were well known in the art at the time of the invention.

Therefore, it would have been obvious for one of ordinary skill at the time of the invention to target a selected genomic locus, either repetitive locus or unique sequences.

One having ordinary skill at the time the invention was made would have been motivated to do so in order to use schistosome as intermediate vector for secretion of desired protein, such as therapeutic protein, into the bloodstream of humans and other susceptible hosts and to facilitate mass production, quality control, termination of therapy at will and dose titration as taught by Miller with reasonable expectation of success.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S/ Chen

Shin-Lin Chen, Ph.D.